REMARKS

The Present Invention

The present invention is directed to a method of inducing an immune response against an antigen in a mammal by inoculating the mammal with two different vectors encoding the antigen.

The Pending Claims

Claims 1-8, and 21-23 are currently pending.

The Amendments to the Claims

Claims 1, 5, 21, and 22 have been amended to point out more clearly and claim distinctly the subject matter of the invention. Claim 23 has been added and is supported by the specification at, for example, page 7, line 22, through, page 8, line 5. Thus, no new matter has been added through amendment of the claims. New claim 23 is copied from U.S. Patent No. 6,663,871 ("the '871 patent"), and thus, if rejected on any ground also applicable to the corresponding claim in the '871 patent, must be approved by the Technology Center Director. *See M.P.E.P. §2307.02.*

The Office Action

Claims 1-8, 21, and 22 have been rejected under 35 U.S.C. § 112, first paragraph, and under 35 U.S.C. § 103. Claims 21 and 22 have been rejected under 35 U.S.C. §112, second paragraph. Reconsideration of these rejections is hereby requested.

Discussion of Rejection under 35 U.S.C. § 112, first paragraph

Claims 1-8, 21, and 22 have been rejected under Section 112, first paragraph. While the Office admits that the specification enables a method of inducing a CTL response in a mammal comprising administering various viral vectors comprising a nucleic acid insert encoding an antigen operably linked to a promoter, the Office apparently is under the mistaken impression that the instant specification does not enable a method of inducing a CTL response in a mammal as a utility. The Office contends that the only stated utility is inducing a therapeutic or prophylactic immune response against an antigen. Based on such contention, the Office concludes that the utility of inducing a therapeutic or prophylactic immune response is not

reasonably enabled by the instant specification. The rejection is traversed for the reasons set forth below.

First, Applicants direct the Office's attention to Housseau et al. (*J. Immuno. Methods*, 266, 87-103 (2002)), Marshall et al. (*J. Clin. Onc.*, 18(23), 3964-3973 (2000)), and Doolan et al. (*Int'l J. Parasit.*, 31, 753-762 (2001)) (all enclosed herewith), for example, as evidence of the utility of the instant invention. Housseau et al. describes a clinical trial wherein patients with melanoma were treated using a heterologous prime-boost regimen, like the regimen described in the instant specification at, for example, page 29, lines 3-28. Marshall et al. describes a clinical trial using two different recombinant vaccines expressing the same antigen in prime and boost regimens to enhance T-cell responses to said antigen. Finally, Doolan et al. describes heterologous prime-boost immunization strategies comprising a malaria-associated antigen to generate a vaccine against malaria. Thus, Doolan et al. describes the use of a non-self antigen in the context of a heterologous boosting immunization, similar to the instant specification.

Although the articles were published post-filing of this application, the clinical experiments described in Housseau et al., Marshall et al., and Doolan et al. are conducted in accordance with the instant claims and specification, thus, providing evidence that the subject claims directed to a therapeutic utility are enabled. It is the Office's obligation to weigh such evidence in determining whether the claimed invention is enabled. Furthermore, the Office should presume that subject matter directed to a therapeutic process that is in clinical trial is reasonably predictive of having the asserted therapeutic utility (*see M.P.E.P. §2107.03*).

Second, the Office contends that the instant specification does not provide adequate guidance to induce a therapeutic or prophylactic immune response against an antigen because β–gal tumors do not correlate to tumors having tumor-associated antigens (TAAs) since β–gal protein is a foreign antigen while TAAs are self-proteins. At the time of filing the instant application, non-self, foreign protein TAAs were known in the art (*see e.g.* Scheffner et al. (*Cell*, 63(6) 1129-36 (1990) (abstract enclosed herewith)). Furthermore, Wang, which was cited by the Office for a rejection under 35 U.S.C. § 103, utilizes β -gal as its model antigen in single dose immunizations comprising the model antigen, and therefore, supports the utility of this application.

In view of the evidence of enablement, the utility rejection should clearly be withdrawn.

Discussion of Rejection under 35 U.S.C. § 112, second paragraph

Claims 21 and 22 have been rejected under Section 112, second paragraph, as allegedly indefinite for failing to point out particularly and claim distinctly the subject matter of the invention. Applicants respectfully disagree with this rejection. However, in order to expedite prosecution of this application and not in acquiescence of the rejection, Applicants have amended claims 21 and 22 to remove the phrase "encoded by both of the first and second recombinant vectors against which an immune response is to be induced." The amendment of claims 21 and 22 is believed to clarify the claims in accordance with the Office's suggestion and not narrow their scope.

In view of the foregoing, Applicants submit that claims 21 and 22 are definite. Accordingly, Applicants respectfully request withdrawal of the rejection under Section 112, second paragraph.

Discussion of Rejection under 35 U.S.C. § 103

Claims 1-3, 5-7, 21 and 22 have been rejected under Section 103 as allegedly obvious in view of and, therefore, unpatentable over Wang (J. Immunol., (1995 May 1) 154 (9): 4685-92). This rejection is traversed for the reasons set forth below.

Applicants respectfully submit that claims 1-3 and 5-7 are not obvious in view of Wang since Wang does not teach inducing an effective immunological response by inoculating with different vectors encoding the same antigen, as does the present invention. The Office contends that one of ordinary skill in the art at the time the invention was made would have been motivated to replace the wild-type vectors used in Wang with the recombinant FPV (fowlpox virus) or VV (vaccinia virus) vectors presented in the instant application. However, no motivation or suggestion to induce an immune response in a mammal by administering two different, recombinant vectors encoding the same antigen can be found in Wang.

The disclosure of Wang is not directed to a prime-boost regimen for immunizations as is the instant application. Rather, Wang tests whether previous immunity to vaccinia virus diminishes the ability of either rVV or rFPV to elicit a CTL response. As indicated on page 4690, Wang is concerned that the previous VV (small pox) immunizations to over 1 billion humans would inhibit both primary and secondary responses to a heterologous protein (antigen) expressed by rVV in those persons. The data presented in Wang provides no evidence of a prime-boost regimen, but rather is testing if an initial immunization with a non-recombinant vector diminishes the ability of a recombinant vector expressing a heterologous protein to elicit a

CTL response, not whether the initial immunization boosts a CTL response. Further evidence indicating that Wang does not relate to a prime-boost regimen can be seen when comparing the last data set in Figure 6 of Wang, wherein the last bar indicates a roughly 50% response after administration of the rFPV, which was secondary to the initial immunization of VV. This level of responsiveness is the same, if not lower, than if only a single immunization of rFPV is administered, as displayed in Figure 2 of Wang. No benefit is demonstrated by the dual immunization regimens described in Wang, rather such regimens assess whether a CTL response is diminished post-immunization. Therefore, Wang does not reasonably suggest a method of administering to a mammal a recombinant vector encoding an antigen followed by administering a different recombinant vector encoding the same antigen to boost the CTL response to that antigen.

Alternatively, Applicants direct the Office's attention to Fig. 5C of Wang and Fig. 1C of the instant application. The Office alleges the data presented in Fig. 1C does not provide evidence of unexpected results when compared to the data presented in Fig. 5C of Wang. Applicants disagree with such a characterization of the data. First, the experiment in Fig. 5C is based on the administration of the same vector (rFPV) twice, which differs from the instant application, whereby two different vectors encoding the same antigen are administered sequentially. Second, a person having ordinary skill in the art would not regard the results of the two experiments as similar. And, in fact, a skilled artisan would find that the claimed method provides advantageous, unexpected results in view of the disclosure of Wang. Specifically, in Fig. 5C of Wang, following the second administration of rFPV only 13% of the mice survived for 80 days. In stark contrast, Fig. 1C of the instant application, shows that after the administration of rFPV followed by administration of rVV, about 60% of the mice survived for over 110 days. The results from Fig 1C, when compared to the data presented in Wang are statistically significant, demonstrating an unexpected result. The Office qualifies this statistical significance by stating that the result is "expected," and Applicants failed to recognize such an expectation because "applicants have not considered the additive effect of rFPV and rVV." *See* Page 10. There is no suggestion in the prior art of the additive effects of using different vectors in accordance with the claimed methods, and further, Applicants consider the result as synergistic rather than additive, which is regarded as unexpected.

Thus, the Office has not established that the prior art provided a motivation or suggestion sufficient to establish a prima facie case of obviousness for the instant invention. The Examiner merely points to the prior art and asserts that although not recited in the prior art, the claimed

method would have been obvious in view of the art. The instant invention was not even "obvious to try," let alone obvious, in view of Wang et al.

In view of the above, Applicants submit that claims 1-3, 5-7, 21 and 22 are not obvious. Therefore, Applicants respectfully request withdrawal of this rejection under Section 103 for obviousness.

Claims 1-8 have been rejected under Section 103 as allegedly obvious over Wang in view of Zhai (Jan. 15, 1996, J. Immunol., Vol. 156, No. 2, pages 700-710). As noted above, the claimed invention is not obvious in view of Wang. Zhai does not cure the deficiencies of Wang. Zhai merely teaches the administration of an adenoviral vector encoding β-gal. Zhai, alone or in combination with Wang, does not teach or suggest the administration of a recombinant vector to a mammal followed by administration of a second recombinant vector encoding an antigen from the first recombinant vector, wherein the second recombinant vector is different from the first recombinant vector. Thus, the obviousness rejection for Wang in view of Zhai cannot stand.

Conclusion

The application is considered to be in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

David J. Schodin, Reg. 41,294
One of the Attorneys for Applicants
LEYDIG, VOIT & MAYER, LTD.
Two Prudential Plaza, Suite 4900
180 North Stetson
Chicago, Illinois 60601-6780
(312) 616-5600 (telephone)
(312) 616-5700 (facsimile)

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